Blood Substitutes

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

847.270.5300
Fax: 847.270.5306

Baxter

May 9, 1997

Docket Number 95S-0158
Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr. rm. 1-23
Rockville, MD 20857

RE: Investigational New Drug Application #6859

Dear Sir/Madam:

In accordance with 21 CFR §312.54 we are enclosing a copy of additional information that has been publicly disclosed, concerning research involving an exception to informed consent at Lehigh Valley Hospital, Allentown, PA. for our clinical trial (BBIND #6859). We include a press release written by the Medical Center (Attachment 1), the resulting article in a local newspaper (Attachment 2), an announcement of Surgical Grand Rounds that appeared on the Lehigh Valley Hospital Home Page on the Internet (Attachment 3), an overview of the presentation of the Grand Rounds given by the Principal Investigator (Attachment 4), the transcript of a news broadcast from NBC Eyewitness News, Scranton/Wilkes-Barre, PA (Attachment 5), the transcript of a news broadcast from Channel 69, Allentown, PA (Attachment 6), articles in local newspapers (Attachment 7 and 8), and a letter to the Editor of a local newspaper, written by the Principal Investigator, a Co-Investigator, and the Administrative Chairman of the IRB. In accordance with 21 CFR §312.54, this information is also being submitted to the IND file.

If there are any questions concerning this information, please contact me at (847)270-5313.

Sincerely,

Todd Marshall for Maulik Nanavaty

Maulik Nanavaty, Ph.D.
Director Regulatory Affairs
Blood Substitutes Program

95S-0158

SUP1

Attachment 1

CONTACT: Constance F. Walker
Public Affairs Manager
(610) 402-3001

Attachment 1

LEHIGH VALLEY
HOSPITAL AND
HEALTH NETWORK

Lehigh Valley Hospital One of Only Seven in Nation to Study Blood Substitute

Allentown, Pa. (Nov. 8, 1996) -- Lehigh Valley Hospital (LVH) is one of only seven sites in the country to study the effectiveness of a new blood substitute, which has the potential to alleviate the growing burden on community blood banks. Beginning this month, the blood substitute will be used as a supplement to blood transfusions in certain elective surgeries. LVH, the only study site in Pennsylvania, was chosen because of high patient volume and infrastructure of research coordinators, nurses, pharmacy and lab technicians to support research studies, according to the study's sponsor Baxter Healthcare Corporation Blood Substitutes Division.

The oxygen-carrying hemoglobin solution is part of a new group of blood substitutes having potentially hundreds of applications, affecting millions of people. The solution has the ability to carry oxygen to tissues and seems to increase blood flow to vital organs and does not have to be typed or cross-matched, thus saving time in operations. In addition, the man-made product is virus-free, reducing the risk of disease transmission, allergic reactions, infection, and immunosuppression.

The one-year study will focus on major surgeries such as hip replacements, bilateral knee replacements and aortic aneurysms. "These surgeries typically require large amounts of blood, which means patients must rely on stored blood products or donate their own blood ahead of time," said Michael Pasquale, M.D., F.A.C.S., chief of trauma at LVH and the study's principle researcher. "As such, the advantages could extend beyond the patients undergoing surgery using the blood substitute. The solution has the potential to relieve the burden constantly imposed on blood banks, thereby benefitting the entire community."

About 50 patients scheduled for elective surgeries will be enrolled in the double blind study with half receiving the blood substitute and half receiving placebo. More than 270 patients have already participated in other hemoglobin solution studies throughout the world with encouraging results.

# # #

PR#29-96

Attachment 2

ALLENTOWN, LEHIGH AND BERKS COUNTIES

THE MORNING CALL

TUESDAY
NOVEMBER 19, 1996
NO. 38.032

50¢

LVH, patients to join blood substitute study

■ Fake blood, called HemAssist, has potential to reduce drain on community blood banks.

By ANN WLAZELEK
Of The Morning Call

It looks like blood, comes from blood and arrives in a clear plastic pouch.

But the dark red, oxygen-carrying liquid is not blood.

It is a blood substitute that will begin coursing its way through the veins of willing elective surgery patients next month and has the potential to reduce the drain on community blood banks.

Lehigh Valley Hospital is one of seven medical centers across the country and the only site in Pennsylvania participating in a study sponsored by the product's manufacturer, Baxter Healthcare Corp., Deerfield, Ill.

Baxter chose LVH because of its high volume of patients and research experience.

LVH officials expect the one-year study to begin the first week of December, when a shipment of the fake blood, called HemAssist, arrives.

Dr. Michael Pasquale, trauma chief and principal investigator of the study at LVH, said the hospital hopes to enroll at least 50 patients at the rate of one per week.

Registered nurse coordinators Wendy Robb and Leslie Bags will seek consent from patients scheduled for hip replacements, double knee replacements and aortic aneurysms — operations that typically require

Please See FAKE Page A6 ▶

MARC LESTER/TI

Nurses Leslie Bags (right) and Wendy Robb (left) examine a blood as Dr. Michael Pasquale observes at Lehigh Valley Ho

FAKE

▶Continued From Page A1

large amounts of blood.

Half of the patients enrolled will receive up to three units, or 750 cubic centimeters, of the substitute; the other half, real blood.

The study is "double-blinded," which means neither the patient nor the surgeon will know which blood product is used before the study is complete, to prevent bias. Only one team of two doctors and three coordinators will know, Robb said.

Although the fake blood and real blood look a lot alike, the substitute has a somewhat thinner consistency, Robb said.

Also, the blood substitute can turn urine pink. Hence the need to tape or otherwise disguise the urinary catheter.

Masking the catheters and blood bags has been the hardest part of the job so far, Robb added. "It is a huge undertaking," she said.

HemAssist, pronounced "heem-assist," is made from expired or outdated human blood. Scientists stripped human hemoglobin, the blood protein that carries oxygen, out of the cell coating that makes it cause allergic reactions and then chemically modified it to stay fresh longer.

"It's been heat purified and pasteurized, so there is a minimal risk of disease transmission," Pasquale said. "The risk is not totally zero," he said, but is smaller than that of real blood.

The fake blood lives in a person's bloodstream for a few days before ceasing to be effective. It does not clot or fight infection like real blood, so it is not a permanent replacement.

However, Pasquale said that by the time a patient's blood substitute starts to fade, the bone marrow will replace it with the real stuff.

The substitute's main function is to deliver oxygen to tissues and organs when time is critical and a suitable match cannot be found. Because fake blood does not have to be typed or cross-matched, its use saves time during operations.

Also, real blood stays fresh about 45 days, and the new substitutes last for up to a year.

There's a tremendous demand for blood substitutes. More than 10 million units of blood are transfused annually in the United States.

Pasquale said he runs short of certain blood types several times a year and has had to give patients

Preliminary studies of HemAssist show it can elevate blood pressure, cause an inflammation of the pancreas, turn urine pink and skin yellow.

Pasquale said the blood substitute is supposed to raise blood pressure because patients who need blood usually need their pressure increased as well. But for the same reason, a patient who has high blood pressure at the time of surgery would not be a good candidate for the study.

Others who would be excluded from the study are under 18, pregnant, burn patients or those who have already donated their own blood in advance of their surgeries.

Once enrolled, a patient can receive the blood substitute within 36 hours of the start of the operation, even after the operation, Robb said.

If more than three units are needed, real blood will follow the substitute, she added.

Care of study participants will not differ from that of other patients, Pasquale said, with the exception of a follow-up visit for an antibody test. Otherwise, all patients will undergo three or four routine blood tests, totaling about 8 tablespoons of blood, he said.

Patients in the study will be followed for seven days or until discharge, whichever comes first.

Robb and Baez do not anticipate having a difficult time finding volunteers from the 1,000 or so patients treated at LVH each year who fit the criteria.

Calling patients on an elective surgery list from three orthopedic practices and two vascular surgery practices, the nurses found one patient interested already. However, his surgery arrived before the blood substitute, Robb said.

A major selling point, she said, is that the fake blood is virtually virus-free. Also, because the product is under investigation, there is no charge for it or the checkups and blood tests that follow.

Medical science has been searching for an effective blood substitute since the 17th century, when doctors tried transfusing everything from animal blood to wine.

The search gained impetus in the 1980s when thousands caught the AIDS virus from tainted blood. But that risk has plummeted today to less than one case per 450,000 pints of blood.

At least six medical manufacturing companies have done early tests on about 800 Americans to see how well the substances carry oxygen to tissues.

In another study, just approved by the U.S. Food and Drug Administration, LVH will be among 21 medical centers nationwide to mass-test blood substitutes on

Attachment 3

NEWS RELEASE

CONTACT: Constance F. Walker, Public Affairs Manager, (610) 402-3001

LEHIGH VALLEY HOSPITAL AND HEALTH NETWORK

DEPARTMENTS & PHYSICIANS
HEALTHY YOU
MEDICAL EDUCATION & RESEARCH
ABOUT US
KID ZONE
MANAGED CARE
WHAT'S NEW

MEDIA ALERT
Lehigh Valley Hospital First to Study Blood Substitute in Trauma Patients

February 10, 1997

WHAT: On February 11, Lehigh Valley Hospital will become the first hospital in the country to study the use of a new blood substitute in trauma patients with severe blood loss. The hospital is holding a special Surgical Grand Round to kickoff this monumental research study, which the U.S. Food and Drug Administration and the Office of Protection of Patient Rights cleared the way for in November by waiving patient consent for research of emergency therapies.

Reporters are invited to attend the Grand Round and learn more about the study from Edward Sloan, M.D., coordinating investigator for the study. Dr. Sloan is from the Department of Emergency Medicine at the University of Illinois, Chicago.

WHEN: Wednesday, Feb. 12, 1:30 p.m. to 2:30 p.m.

WHERE: Lehigh Valley Hospital, Cedar Crest & I-78, Auditorium

BACKGROUND: The oxygen-carrying hemoglobin solution is part of a new group of blood substitutes having potentially hundreds of applications, affecting millions of people. Trauma-related injuries are the number one cause of death among Americans ages 1-45.

The blood substitute has significant applications in trauma situations such as increased blood flow to vital organs, decreased time stabilizing patients since the does not have to be typed or cross-matched, and decreased risk of contamination.

Based in Allentown, Pa., LVH is a community-based health care institution and a regional referral center for trauma, burn, kidney transplant, perinatal, cardiac and cancer care. It has more than 660 patient beds and a medical staff of 700 working in more than 50 specialities. As Pennsylvania's oldest and largest teaching hospital, LVH is the chief clinical campus of Penn State University's Hershey Medical School.

LVH is a division of Lehigh Valley Health Network, which also includes home health, hospice, pharmacy, durable medical equipment and laboratory services, among others. The network is a member of PennCARE, a provider-led, integrated health care delivery system comprised of nine hospitals in eastern Pennsylvania and participating members of their medical staffs.

Attachment 4

Overview of Grand Rounds presentation at Lehigh Valley Hospital- February 12, 1997

General Greeting and Introductions- Mark Cipolle, MD, PhD
- Principal Investigator for THS study

Introduction to DCLHb- Ed Sloan, MD, MPH (presenter)
- Chemical structure- cross-linked to stabilize
- Hemoglobin based oxygen carrier
- Pressor/perfusion properties

Preclinical Overview
- Product properties seen in preclinical studies including increases mean arterial pressure, restores base deficit, restores lactate levels, restores subcutaneous PO2, restores mucosal PO2, reduces bacterial translocation, increases oxygen consumption, reduces mortality and perfusion properties
- Review of specific data from preclinical studies that support each of the above

Hemorrhagic Hypovolemic Shock Study Overview (completed study)
- Study design
- Summary of patient population
- Summary of safety findings- no increase rate of complications or adverse events
- Efficacy findings- patient population not sufficient to determine efficacy

Traumatic Hemorrhagic Shock Study Overview
- Introduction to trauma and the impact on society
- History of protocol development
- Study design
- Patient care- all standard therapies will be provided
- Study inclusion/exclusion criteria
- Timelines mandated by protocol
- Dosing and infusing
- Blinding of study, investigators blinded prior to randomization, not blinded during infusion
- Endpoints and analyses- 28 day mortality, morbidity using the MOD score, 48 hour mortality
- Laboratory issues
- Exception from informed consent issues and consent to continue
- Role of the IRB- community consultation and public disclosure

Overview of Grand Rounds presentation at Lehigh Valley Hospital- February 12, 1997 (cont.)

Hemoglobin Based Oxygen Carriers (HBOCs)

Old paradigm- blood substitutes

New paradigm- hemoglobin-based oxygen carriers

HBOCs potential uses- trauma, blood loss, surgery, MI, stroke, cancer, radiation therapy, cardiopulmonary bypass, sepsis, dialysis, sickle cell disease, anemia

Summary

Trauma important issue

Study to determine if DCLHb will improve survival

Attachment 5

Transcript

DATE February 12, 1997
TIME 11:00-11:35 PM
STATION WBRE-TV(NBC) Ch. Twenty-Eight
LOCATION Scranton/Wilkes-Barre, Pa.
PROGRAM Eyewitness News Nightbeat

Female co-anchor:

A first of its kind medical study in our area may be the key to saving time and lives in emergency situations. An Allentown hospital is the first in the country to use fake blood. That's right fake blood. Healthbeat reporter Diana Penna takes a look at the potential benefits.

Diana Penna reporting:

It looks like real blood but it isn't. Now researchers are hoping it can help patients suffering from blood loss and shock ...(Inaudible) severe trauma. The blood ...(Inaudible) is actually hemoglobin released from human blood cells. Hemoglobin is the iron carrying protein that gives blood its red color. Solutions like this are already proven oxygen carriers and in emergencies, a boost in oxygen delivery is crucial.

Unidentified Speaker: This new therapy seems to improve flow to vital organs.

Penna: In a trauma situation, sometimes minutes even seconds can mean the difference between life and death. This blood substitute would also cut down on the time limit to stabilize a patient because the man-made blood doesn't need to be typed or cross matched. The fake blood is made up of hemoglobin from real donated blood so there's also less risk of contamination like AIDS or other viruses because it's already been screened.

Unidentified Speaker #2: In addition, because the molecule doesn't exist within the red blood cell, it can be purified or treated in a way that makes it far less likely that there would be any transmission of viruses as a result of the infusion of this ...(Inaudible).

Penna: Dr. Edward Sloane(?) along with Dr. Mark Shipley(?) are the principle investigators for the nationwide study starting here in Lehigh Valley Hospital

in Allentown. The hospital is already using the blood substitute in elective surgery like knee and hip surgery. Past studies found it safe. This phase will determine how effective it is.

That's the Healthbeat. I'm Diana Penna.

Female co-anchor: Now, the Lehigh Valley Medical Center is the first of about thirty sites testing this fake blood nationwide so it's quite an honor really.

Male co-anchor: Yeah. Actually, it is an interesting project. The wave of the future.

# # #

Attachment 6

VIDEO MONITORING SERVICES OF AMERICA, L.P.

Los Angeles (818) 888-8111 | Chicago (630) 940-1151 | Philadelphia (215) 568-4900 | San Francisco (415) 543-3261 | Detroit (810) 347-8230
Boston (617) 266-2121 | Dallas (214) 644-8500 | Washington (202) 393-7116 | Houston (713) 780-1455 | Miami (305) 576-1581
Denver (303) 733-8000 | Hartford (860) 236-8822 | San Diego (619) 644-1400

Transcript

DATE February 12, 1997
TIME 7:00-7:30 PM
STATION WFMZ-TV(IND) Channel 69
LOCATION Allentown, Pa.
PROGRAM Channel 69 News

Rob Vaughn, anchor:

Lehigh Valley Hospital is leading the way in a ground-breaking study. Hospital officials held a conference this afternoon to kick off a research study in which they'll be using a new blood substitute to treat trauma patients with severe blood loss. Lehigh Valley is the first hospital in the country to use the blood substitute. It has significant applications in trauma situations such as increased blood flow to vital organs and it has a decreased risk of contamination. (Footage shows conference held at Lehigh Valley Hospital)

# # #

Attachment 7

USINESS
Day-Timers CEO joins NovaCare
PAGE B11
SIDE
4 apply for seat on ASD board
PAGE B3

THE MORNING CALL
Local
ALLENTOWN, LEHIGH AND BERKS COUNTIES
THURSDAY, FEBRUARY 13, 1997
Page 10

LVH to try out new blood product

Some ill and injured patients will receive HemAssist plus standard treatment.

By ANN WLAZELEK
Of The Morning Call

Beginning next month, some Lehigh Valley Hospital trauma patients will receive an experimental blood product whether they want it or not.

But all 25-30 seriously ill and injured patients enrolled in the study over the next year should benefit, the study's chief medical researcher said Wednesday.

Dr. Edward Sloan, an emergency medicine specialist at the University of Illinois, Chicago, said every patient will receive standard life-saving treatments, including real blood and oxygen.

In addition, half the patients in the study will get up to one liter of the oxygen-carrying experimental red liquid, called HemAssist, which Sloan said appears to be safe and more effective than blood at delivering oxygen to vital organs, tissues and cells.

The other half of the study group receives an inactive saline solution instead of HemAssist. According to Sloan, those patients benefit from the added attention of doctors and nurses involved in the study.

Does that mean there is no risk to the patient who gets the experimental treatment?

"No," Sloan told reporters after lecturing to doctors, nurses and other medical personnel in the auditorium of the Salisbury Township medical center.

"Any time a patient receives a new drug there are risks," he said. "The important thing is to make sure the risks are commensurate with the benefits."

Please See BLOOD-DRUG Page B6 ▶

BLOOD-DRUG

▶Continued From Page B1

HemAssist is "virtually virus-free," Sloan said. He deemed the product as safe as albumin, which doctors have used for 30 years to expand the volume of fluid in patients with severe blood loss, without evidence of AIDS or hepatitis B transmission.

Sloan said the nation's blood supply is very safe and HemAssist is made from expired human blood. Risk of viral transmission is further reduced by a heating and purification process, he said.

Earlier studies on pigs, rats and healthy and sick people suggest that the altered blood product restores and maintains blood pressure better than the real thing.

While some doctors and patients worry that the rise in blood pressure could cause other complications, Sloan said studies showed the pressure did not rise abnormally high.

The effects of the experimental product last days to weeks, he said, with the body making new blood cells to replace what was lost.

Because consent cannot be obtained from most trauma patients, who enter the emergency room unconscious, officials expected some objections. But LVH received only six calls after the hospital's participation was announced last month. Only one caller was critical, according to a nurse coordinator.

In November, the federal Food and Drug Administration waived patient consent in studies of emergency therapies, claiming the benefits outweigh the risks.

This is LVH's second study involving HemAssist. In December, the hospital was one of seven in the nation to start using the solution on consenting elective surgery patients.

Sloan said the benefits of HemAssist could extend well beyond trauma patients. Someday it may reduce or replace real blood transfusions in surgery, limit damage to stroke patients, enhance the ability to eliminate cancer with radiation and reduce heart-lung machine complications in bypass patients.

In this study, however, Sloan said the purpose is to prove that HemAssist actually does benefit patients and save lives.

Each year, 150,000 Americans lose their lives to auto accidents, shootings, stabbings and major traumatic illnesses at a cost of $50 billion in treatment and lost productivity, he said.

"It is immediate, catastrophic and the leading cause of death in young people," he said.

LVH's principal investigator, Dr. Mark Cipolle, expects delivery of the experimental blood product within a week and enrollment to begin in the next month.

Attachment 8

The Philadelphia Inquirer

Sunday, February 16, 1997

Medical pioneer will be unaware

Lehigh Valley Hospital has been chosen for the first use of an artificial blood. The patient won't have to give consent.

By Donna Shaw
INQUIRER STAFF WRITER

ALLENTOWN — Any day now, a bleeding, severely injured patient will be whisked into Lehigh Valley Hospital and enter not only the emergency room, but medical-research history.

Unconscious and close to death, the patient will receive an experimental blood substitute that doctors hope will save many lives.

Scientists have been trying for decades to develop artificial blood, until recently with little success. Now, Lehigh Valley has been chosen as the first hospital in the nation to administer such a product to a trauma patient — without the patient's consent.

It also will mark what researchers believe is the first time, under new government rules, that an unapproved medicine is administered to someone who is near death and unable to agree to the treatment.

The new policy, which became effective in November, allows emergency-room physicians to use "promising experimental drugs and medical devices" only on patients in life-threatening situations. It has the endorsement of a broad range of scientific, industry, medical-ethics and patient organizations.

The theory is that the policy makes cutting-edge therapies available to people who most likely would want and benefit from them if only they could give informed consent. The groups say it also sets out clear rules that provide more, not less, protection for patients.

Not everyone agrees. The critics range from some minority groups, who are fearful they will be targets of experiment-happy scientists, to none other than "suicide doctor" Jack Kevorkian.

In an opinion article published last week, Kevorkian compared the new policy to World War II Nazi atrocities. "What we have just taken is a fast ride down the slippery slope, right to the absolute depths," he wrote.

Food and Drug Administration officials say such rhetoric is a gross distortion of the facts.

"I know there are some people ... who look at this as a lessening of the rules," said FDA spokesman Don McLearn. "We don't look at it this way."

In fact, emergency-room research conducted upon unconscious patients is not new. Many modern life-saving procedures, such as cardiopulmonary resuscitation and electrical defibrillation, were developed that way.

In those cases, approval generally

See TESTS on D9

Sunday Business

Unwitting patient will be pioneer in a hard test of blood and policies

TESTS from D1

was an isolated event, granted by an institutional review board (IRB) at an individual hospital. That made it difficult for doctors to conduct the kind of coordinated, multicenter research that today is considered the standard. Nor was there clear federal guidance.

The FDA, which governs clinical research, had rules that allowed a waiver of informed consent only in individual, limited cases. That was in conflict with the rules established by the National Institutes of Health, which oversees IRBs.

In 1994, a coalition of emergency-room researchers issued a statement calling upon the government to rewrite its rules. The federal guidelines then in effect "do not adequately guide IRBs in their considerations of emergency research protocols and do not adequately protect human subjects involved in emergency research," the coalition said.

The coalition recommended that the FDA and NIH develop compatible policies that explicitly addressed emergency-room research and implemented patient safeguards.

Among the organizations endorsing the statement were the American Academy of Pediatrics, the American College of Emergency sociation, the National Head Injury Foundation, and the Applied Research Ethics National Association.

The FDA and NIH policies enacted in November echo many of those earlier recommendations, calling for experimental treatments to be used only in narrow circumstances. Among them: Any such research must be approved by an independent physician and a hospital review board that includes lay people from the community.

In the research about to begin at Lehigh Valley, all patients enrolled in the study will receive standard treatment in addition to the new blood substitute, designed to boost oxygen levels, researchers said.

Doctors involved in the plan say that, so far, the public's reaction has been overwhelmingly favorable.

"People tend to view it as an opportunity to get the best care," said Mark Cipolle, Lehigh Valley Hospital's associate chief of trauma and the study's principal researcher.

Said Edward Sloan, the University of Illinois physician who is coordinating the research nationwide: "Most of the reaction is positive. . . . At least 90 percent are happy with the process."

The blood substitute, a Baxter Healthcare Corp. product called HemAssist, already is being tested in

have given their permission in advance of treatment. The new, emergency-room trials will take place over the next 12 to 18 months, at 20 or more hospitals across the country. By the time the research is completed, approximately 850 trauma patients will have taken part, according to the plan.

After they are conscious, the patients are to be informed that they received an experimental medicine. Those who object to taking part in the research will be dropped from the study, and their data won't be included, according to Cipolle and Sloan.

Sloan noted that, even with treatment, the study subjects will be so severely injured that about 40 percent likely will die.

Attachment 9

The Morning Call (Allentown)

February 28, 1997, Friday, FIFTH EDITION
SECTION: COMMENT, Pg. A8

LENGTH: 591 words

HEADLINE: PATIENT RIGHTS ARE BEING PROTECTED

BYLINE: The Morning Call

BODY:
To the Editor:

As representatives of Lehigh Valley Hospital, it is important to respond to the Feb. 13 article describing our participation in an upcoming clinical trial. The study is designed to determine whether the hemoglobin-based, oxygen-carrying solution Diaspirin Cross-Linked Hemoglobin will improve the care of patients who are in shock from bleeding. While we appreciate the media coverage of what we consider to be an extremely important study, we feel there are a few points in the article which need to be clarified.

Patients who are in shock from bleeding and arrive at the trauma center will be randomized to receive either the hemoglobin-based oxygen solution or the placebo, saline. The new solution or the placebo need to be given within one hour of arrival to the trauma center. We anticipate that most patients eligible for this study will be unable to give their own consent due to their medical condition. Because the onset of trauma is unpredictable, a legally authorized representative may not be available to provide consent for the patient and we may be unable to contact a family member before infusion of the solution is required.

To test the effectiveness of this new therapy, which will be given as an addition to other standard life-saving treatments, it is necessary to meet guidelines developed by the Food and Drug Administration for conducting emergency research with a waiver of informed consent. The FDA, in cooperation with the National Institutes of Health, with input from both the scientific and lay communities, has been working for two years to develop these guidelines. These new regulations clarify guidelines that will allow a study to be conducted with an exception or waiver from the requirement of obtaining written informed consent only in those rare circumstances where the patient cannot provide consent and the nature of the patient's medical condition requires immediate treatment. We feel the new policy provides more, not less, protection for patients.

The Institutional Review Board at each participating center is responsible for insuring the protection of patients enrolled in clinical trials.

As soon as the patients themselves, legal representative, or family members are able to participate in the informed-consent process, the study will be thoroughly explained to them. Patients of families who do not wish to participate in the study will not be enrolled. Additionally, if a patient or family member wishes to drop out of the study after enrollment he or she will be allowed to do so at any time.

We would like to assure readers that as investigators of an exciting new trial, we are committed to performing the best study possible with strict adherence to the guidelines set forth by the FDA and our institutional review board. As a Level I Trauma Center, our commitment is to advance the care of trauma patients in the community and to provide our patients with the best chance of recovery. It is a privilege to provide the best care available to our patients, and we look forward to carrying this concept into the 21st century.

MARK D. CIPOLLE, MD, PHD

PRIMARY INVESTIGATOR, DCLHB STUDY

Associate Chief of Trauma/Surgical Critical Care

Lehigh Valley Hospital

MICHAEL PASQUALE, MD

CO-INVESTIGATOR, DCLHB STUDY

Chief, Division of Trauma/Surgical Critical Care

Lehigh Valley Hospital

KEVIN SIDDONS, MED

ADMINISTRATIVE CHAIRMAN, INSTITUTIONAL REVIEW BOARD

Lehigh Valley Hospital

LOAD-DATE: March 4, 1997

Blood Substitute

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Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

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Fax: 847.270.5306

Baxter

0270 '97 APR 23 A9:41

April 21, 1997

Docket Number 95S-0158
Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr. rm. 1-23
Rockville, MD 20857

RE: Investigational New Drug Application #6859

Dear Sir/Madam:

In accordance with 21 CFR §312.54 we are enclosing a copy of the information that has been publicly disclosed by the Institutional Review Board (IRB) at Christiana Hospital, Medical Center of Delaware, Newark, DE, concerning research involving an exception to informed consent for our clinical trial (BBIND #6859). We include the press release written by the Medical Center (Attachment 1), an article in the local newspaper resulting from an interview with the principal investigator (Attachment 2), an article in the internal hospital newspaper (Attachment 3), a letter from the Research Coordinator and Principal Investigators to the Medics (Attachment 4), a letter from the Research Coordinator and Principal Investigators to the Hospital Personnel that included the protocol synopsis (Attachment 5), public meeting announcements in the local newspaper on 3 separate days (Attachment 6), and the agenda for the public meetings and the write-up of the questions asked by the public (Attachment 7). In accordance with 21 CFR §312.54, this information is also being submitted to the IND file.

If there are any questions concerning this information, please contact me at (847)270-5313.

Sincerely,

Maulik Nanavaty, Ph.D.
Director Regulatory Affairs
Blood Substitutes Program

95S-0158

RPT 1

Attachment 1

The Medical Center of Delaware

Contact: Michele A. Schiavoni
302-428-2122
March 4, 1997

WILMINGTON, Del. -- The Medical Center of Delaware (MCD) will begin conducting a study of a new, potentially life-saving treatment for patients suffering from severe traumatic injuries. The study has been approved by the Institutional Review Board (IRB) of the Medical Center of Delaware. The IRB is a committee which reviews research studies to see that they are well designed with safeguards for patients and the risks are reasonable in relation to the potential benefits. Randomly selected critically ill patients in shock, will be given Diaspirin Cross-Linked Hemoglobin, a blood solution, in addition to standard emergency treatment. The clinical trial will be supervised by the U.S. Food and Drug Administration, for its effectiveness in treating or preventing the harmful effects of blood loss and shock caused by severe trauma.

According to Glen H. Tinkoff, M.D., the Medical Center's director of Trauma Service, "We believe there is sound scientific evidence to show that this new blood solution may improve the survival of patients suffering from severe traumatic hemorrhagic shock and reduce their risk of prolonged serious illness. The results of our testing and similar clinical studies around the country could have profound impact on the future of emergency medical care and could very possibly help us to save more lives."

A very small number of emergency patients (20-30) will receive the blood solution or saline, according to strict study criteria. The study will focus on men and women who are believed to be at least 18 years old and who are at the greatest risk of death from severe traumatic injury. The study solution will be administered as additional therapy to the best known treatment for hemorrhagic shock, including emergency surgery and the infusion of resuscitation fluids and blood.

Possible side-effects include high blood pressure, hemolysis, jaundice, stomach, back and muscle pain, nausea and vomiting, "but the possible benefits of using the solution in severe trauma cases potentially outweigh the risk of these side-effects in deciding to proceed with the clinical study," according to Tinkoff.

Patients who decide not to participate or are not eligible to enroll in the study will continue to receive the best possible medical care critically injured trauma patients currently receive at the Medical Center. Patients, due to the nature of their condition and their critical need for immediate treatment, may not be able to give their consent for participation in the study. An exception from consent, (known as waived consent) authorized by the U.S. Food and Drug Administration (21 CFR 50.24), will be used when it is not feasible to obtain informed consent from the patient, a family member or a legally authorized representative. A patient may withdraw or be withdrawn from the study at any time, without influencing his or her medical care. MCD's Level One Trauma Center at Christiana Hospital is one of 35 centers in the United States to test the Diaspirin product, manufactured by Baxter Healthcare Corporation, Deerfield, IL.

Anyone who has questions about the study may contact Robert O'Connor, M.D., Director of Research, Emergency Medicine, Medical Center of Delaware, at (302) 733-4700; or Glen Tinkoff, M.D., Director of Trauma, Department of Surgery, (302) 733-4700. Monday - Friday from 9 a.m. and 4.30 p.m. If you have questions about your rights as a potential participant in this study before treatment, contact Jerry Castellano, Pharm.D., Director of the Institutional Review Board (IRB) of the Medical Center of Delaware (302) 428-4103

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Attachment 2

Saturday, March 8, 1997, Section B

Have a Local news tip? Call 324-2774.

Local

▶ CROSSROADS: Gas stations with repair garages are becoming a thing of the past B3

Victims of trauma to test blood solution

By JANE HARRIMAN
Staff reporter

Trauma victims dying from loss of blood and shock will get a second chance thanks to a revolutionary blood solution to be tested this month at the Medical Center of Delaware's Christiana Hospital.

Diaspirin Cross-Linked Hemoglobin contains pure hemoglobin, the chemical in red blood cells that carries oxygen through the body.

Diaspirin raises oxygen levels in patients' bodies, and also, for reasons not understood, gives a temporary boost to falling blood pressure, said Dr. Glen H. Tinkoff, director of Trauma Service at the medical center.

The medical center's regional trauma center at Christiana is one of 30 sites chosen for the test of 850 patients because it has a high volume of the kind of patients needed.

While Diaspirin — not related to aspirin — may help save many of the more than 100,000 lives lost annually to trauma, it also holds enormous potential in many other areas of medicine, Tinkoff said.

For example, it may be used for the thousands of patients who hemorrhage from childbirth, ulcers or abdominal aneurysms.

It also may reduce the need for blood transfusions for surgical patients, and provide therapy for the 0.3 percent of African-Americans with sickle cell disease.

About 40 percent of trauma patients in "hemorrhagic shock" die despite treatment. They lose so much blood that their circulatory system collapses and oxygen cannot reach vital organs.

Those who are revived enough to go into intensive care often die from brain damage or failure of the kidney or other organs, Tinkoff said.

"I am tired of seeing these people die. ... I've followed this solution development over the past four years and I am intrigued by it," Tinkoff said.

"I think it's going to save lives. ... I think it's going to be the 'sliced bread' of trauma care."

See BLOOD — B5

IF YOU GO

The Medical Center of Delaware will have two public meetings on the use of Diaspirin Cross-Linked Hemoglobin:

- 7 p.m. March 18 at Riverside Hospital Medical Arts Complex.
- 7 p.m. March 19 at the emergency conference room in Christiana Hospital.

Registration is requested. Call 428-4100.

The News Journal, Wilmington, Del.

Blood: Trauma aid tests due

FROM PAGE B1

Patients in shock are now put on a ventilator and given oxygen, blood cells, saline solution, medications and surgery, Tinkoff said. Those eligible for the trial will get Diaspirin or a placebo, an inert preparation used as a control.

New U.S. Food and Drug Administration rules allow a life-saving investigational treatment to be given to patients too ill to give their informed consent, said Jerry Castellano, director of the medical center Institutional Review Board. The board must approve any research project proposed to make sure it is safe for patients.

If a patient is under waiver and wakes up or if a relative who could give informed consent for him arrives at the hospital, staff will explain the treatment and withdraw treatment if consent is denied.

About 17,000 accident victims — out of 65,000 emergency room visits — were admitted to Christiana Hospital last year. More than 1,500 — about five a day — had injuries serious enough to be labeled trauma. The definition usually involves serious injuries to more than one body system. About 75 percent of trauma patients are male, ages 24 to 35. Many have been drinking, and most have been in motor vehicle accidents.

About one trauma patient a day at Christiana last year had highly critical multisystem injuries requiring a "trauma code," an immediate response by a team of trauma experts. Of those patients, 40 were in hemorrhagic shock and would have been eligible for the Diaspirin trial, Tinkoff said.

Patients must be at least 18 and have no known head injury, and have been at the hospital no more than 30 minutes to be considered for the trial. After eligibility is determined, patients will randomly be given either Diaspirin or a placebo.

Diaspirin has minor side effects: As the hemoglobin is broken down by the body, the patient's skin gets yellowish, like a fading bruise.

Diaspirin is made from donated blood, but no blood components other than the natural chemical hemoglobin is in the solution. Blood typing is not necessary. Also, the hemoglobin is pasteurized and any virus or bacteria in the donated blood has been killed.

Castellano and Tinkoff said it would be difficult to come up with reasons why an eligible patient should turn down the blood solution, and agreed they'd give it to a loved one "in a heartbeat."

Two other area hospitals are testing Diaspirin: the former Medical College of Pennsylvania Hospital, now part of the Allegheny Health System in Philadelphia, and Lehigh Valley Hospital in Allentown, Pa.

Diaspirin is made by Baxter Healthcare Corp. in Deerfield, Ill. It is given without charge in the trial. The eventual cost is not yet known.

Attachment 3

MEDICAL CENTER DELAWARE

FOCUS

An Employee Publication

March 12, 1997
Volume 8, No. 6

Published every two weeks by the Medical Center of Delaware Public Affairs Department, P.O. Box 1668, Wilmington, DE 19899.

New name, new look in the works

Have you noticed how many organizations, such as banks and telecommunications firms, have changed their names in recent years? It's happening throughout the country, and health-related organizations are among those changing their identities.

As MCD becomes a more fully integrated multi-state health system, we need to update our name and image to clearly communicate to our patients and to our community the growth of our organization, the expansion of our geographic reach and our many strategic capabilities.

"We are no longer simply a hospital provider organization," explains Phil Wescott, senior vice president for Marketing/Public Affairs/Development/Government Relations/Volunteer and Student Services Administration. "We are increasingly involved in every aspect of improving our community's health, as well as the funding of care through First State Health Plan and Mid-Atlantic Health Systems." A strong branding program and new corporate identity will go a long way toward "clarifying the relationships among our hospitals and other business units, including VNA, our primary care physicians and the Holding Company," he points out. "In the managed care marketplace, we will need a strong brand name and clear identity to compete against other large organizations for managed care contracts."

Working with Public Affairs, Monigle and Associates—a national corporate identity consulting firm with more than 25 years experience in the health care industry—has begun to research and analyze our market and our organization. Once a new name is agreed upon and thoroughly tested in the marketplace, Public Affairs will launch a comprehensive new corporate identity program.

The new system name will be embodied in a new logotype and a new look that will be applied to all advertising, publications, signs, letterhead,

New name (continued)

business cards, and electronic communications. These changes will begin to be phased in by the end of the year. *Focus* will keep you posted as the transition process is completed.

"Our objective," Wescott says, "is a clearer, more descriptive, distinct and geographically adaptable name that will stick in the minds of our employees, payers and the community at-large."

Trauma Center researches use of new investigational drug

A new, potentially life-saving treatment for patients suffering from a severe traumatic injury is under study in the Trauma Center at Christiana Hospital. Randomly selected critically ill patients in shock will be given Diaspirin Cross-Linked Hemoglobin, a blood solution, in addition to standard emergency treatment. The clinical trial will gauge the solution's effectiveness in treating or preventing the harmful effects of blood loss and shock caused by severe trauma.

"We believe there is sound scientific evidence to show that this new blood solution may improve the survival of patients suffering from severe traumatic hemorrhagic shock and reduce their risk of prolonged serious illness," says Glen H. Tinkoff, M.D., the Medical Center's Director of Trauma Service. "The results of our testing and similar clinical studies around the country could have profound impact on the future of emergency medical care and could very possibly help us to save more lives."

The study has been approved by the Medical Center's Institutional Review Board (IRB). The IRB reviews research studies to ensure that they include safeguards for patients and that the risks are reasonable in relation to the potential benefits.

Because of the nature of their condition and their critical need for immediate treatment, some patients may not be able to give their consent for participation in the study. For the purposes of this clinical research, the FDA has authorized an exception from consent—known as "waived consent"—when it is not feasible to obtain informed consent from the patient, or from a family member or a legally authorized representative. A patient may withdraw or be withdrawn from the study at any time.

(Continued on page 5)

Trauma (continued from page 2)

MCD's Level One Trauma Center at Christiana Hospital is one of 35 centers in the United States to test the Diaspirin product, manufactured by Baxter Healthcare Corporation. If you have questions about the study, call Robert O'Connor, M.D., Director of Research, Emergency Medicine, at 733-4700, or Glen Tinkoff, M.D., Director of Trauma, Department of Surgery, at 733-4700. If you have questions about your rights as a potential participant in this study before treatment, contact Jerry Castellano, Pharm. D., Director of the Institutional Review Board, at 428-4103.

Buddy Elmore promoted

Buddy Elmore, the Medical Center's Senior Vice President for Finance, has been promoted to the system-wide position of Senior Vice President and Chief Financial Officer/Managed Care.

"In this new position, Buddy will have overall leadership responsibility for System Financial Management, while assuming a significant leadership role in assisiting MCD and our integrated healthcare system develop and implement a dynamic managed care strategy that will position the IHS for near- and long-term success," noted President and Chief Executive Officer Charles M. Smith, M.D., M.P.H., in announcing the promotion on March 3.

WH campus construction update

The second phase of the Wilmington Hospital campus construction upgrade will begin the week of March 17. Please see the attachment to this issue for a description and map outlining the changes planned for the weeks ahead.

Lord & Taylor donates $5,000

Along with the hoopla surrounding the grand opening of the new Lord & Taylor department store at Christiana Mall on March 5, came a generous donation to the Medical Center's Cancer Outreach Program. Marshall Hilsberg, Lord & Taylor's chairman and chief executive officer since 1986, presented a $5,000 check to MCD Executive Vice President and Chief Operating Officer James F. Caldas at a recognition ceremony that morning before the new store's formal opening.

Attachment 4

Christiana Hospital

MEDICAL CENTER OF DELAWARE

4755 Ogletown-Stanton Road
P.O. Box 6001
Newark, Delaware
19718

302-733-1000

Medical Center of Delaware Research Institute
(302) 733-4166

11 Apr 1997

Dear Medic:

This purpose of this letter is to inform you of a new clinical research study which will be implemented at the Chrisitiana Hospital, Medical Center of Delaware. This study is projected to begin at the end of April and last approximately 18 months.

This research study involves an investigational blood substitute, called Diasprin Cross-linked Hemoglobin. This hemoglobin solution will be administered to randomally selected trauma patients who are in severe hemorrhagic shock from a traumatic injury.

To comply with the study's protocol we will be extracting, from the medic report, pre-hospital data such as the glascow coma scale, vital signs, and administered pre-hospital fluids and medications.

If you should have any questions, please do not hesitate to call me at (302) 733-4166.

Thank you for your attention to this matter.

Sincerely,

Patty McGraw, RN, Research Coordinator
Glen Tinkoff, MD, Director of Trauma, Principal Investigator
Robert O'Connor, MD, Director of Emergency MedicineResearch, Principal Investigator

PM/nlw

PLEASE POST

Medical Center of Delaware Research Institute
One of the Research Institutes of the Medical Center of Delaware

Attachment 5

Christiana Hospital

MEDICAL CENTER OF DELAWARE

4755 Ogletown-Stanton Road
P.O. Box 6001
Newark, Delaware
19718

302-733-1000

Medical Center of Delaware Research Institute
(302) 733-4166

27 Mar 1997

Dear Director and Nurse Manager, Emergency Department:

This purpose of this letter is to inform you of a new clinical research study which will be implemented at the Christiana Hospital, Medical Center of Delaware. This study is projected to begin at the end of April and last approximately 18 months.

This research study involves the administration of an investigational blood substitute, called Diaspirin Cross-linked Hemoglobin, to randomally selected trauma patients who are in severe hemorrhagic shock from a traumatic injury.

Enclosed is a protocol synopsis for your review.

If you should have any questions, please do not hesitate to call at (302) 733-4166.

Thank you for your attention to this matter.

Sincerely,

Patty McGraw

Patty McGraw, RN, Research Coordinator
Glen Tinkoff, MD, Director of Trauma, Principal Investigator
Robert O'Connor, MD, Director of Emergency Medicine Research, Principal Investigator

PM/nlw

03 October 1996

Protocol Synopsis

"The Efficacy Trial of Diaspirin Cross-linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock"

Introduction

Death from trauma frequently results from shock that is refractory to resuscitation efforts. These efforts typically involve rapid infusions of large volumes of crystalloid solutions. This standard of therapy has been brought into question by recent clinical studies utilizing small volumes of hypertonic saline-Dextran solution (Mattox et al. 1991, Ann Surg 213:482-91), or no volume replacement until definitive surgical treatment (Bickell et al. 1994, N Eng J Med 331:1105-1109).

Trauma-related mortality has been correlated with the magnitude of base deficit. According to Siegel et al. (Arch Surg 1990, 125:498-508), a base deficit of 11.8 mmol/L predicts a mortality of 50% in trauma patients presenting with pelvic fractures or blunt liver trauma. Rutherford et al. (J Trauma 1992, 33:417-423) reported a mortality rate over 40% in trauma patients with base deficits in excess of 15 mmol/L. This study of 3791 trauma patients also showed a sharp, corresponding rise in mortality rates from 20% to 40% over the base deficit range of 10 to 15 mmol/L.

The above findings suggest that the current practice of restoring blood pressure through large volume crystalloid infusion may be suboptimal in traumatic hemorrhagic shock patients. These traumatic shock patients, especially those with large base deficits, are at greatest risk, and warrant being studied with a controlled clinical trial with a low volume pressor/perfusion agent such as DCLHb.

Initial DCLHb Hemorrhagic Shock Trial

The initial prospective, randomized, escalating dose clinical trial of DCLHb in hemorrhagic shock studied the infusion of normal saline (NS) or DCLHb in class II-IV shock patients within four hours of the shock episode. The trial was divided into three dose ranges, 50 mL (71 mg/kg), 100 mL (143 mg/kg), and 200 mL (286 mg/kg). Each dose included approximately 40 patients (20 NS, 20 DCLHb). Patient enrollment for this clinical trial was completed in May 1995 with a total population of 139 patients, 71 (51%) of whom received DCLHb.

No increase in the rate of complications or toxicities in patients who received DCLHb were observed during the trial. Specifically, renal insufficiency and failure were not more common in DCLHb-treated patients. Overall mortality rates, complications and adverse event rates did not differ in the DCLHb and control groups. These findings, and findings from several other DCLHb trials at different doses (750-1200 mLs), suggest that DCLHb infusion will have a favorable risk/benefit profile in severely injured patients.

Study Design

This will be a multicenter, randomized, placebo-controlled (normal saline) study. Inclusion in this protocol will not interfere with the provision of any standard trauma therapy.

Primary Clinical Benefit Endpoint

- Clinically and statistically significant reduction in 28 day mortality.

Secondary Clinical Benefit Endpoint

- Clinically and statistically significant reduction in morbidity.
- Clinically and statistically significant reduction in 48 hour mortality.
- Clinically and statistically significant reduction in 24 hour lactate levels.

Patient Population

The study population will be a small subset of trauma patients with persistent, severe, hypoperfusion despite aggressive pre-hospital therapy. To properly investigate the mortality and morbidity outcomes in this protocol, 500 to 1000 mL DCLHb or the saline control will begin being infused no later than 30 minutes after meeting the entry criteria and within 60 minutes of presentation to the emergency department in approximately 850 patients meeting the following inclusion criteria:

1. Males or females 18 years of age or older
2. Evidence of hemorrhage
3. Tissue hypoxia and cellular hypoperfusion shown by:
   - Systolic blood pressure ≤ 90 and pulse ≥ 120 or,
   - Systolic blood pressure ≤ 90 and pulse < 60 with a pre-terminal rhythm (junctional or idioventricular) or,
   - Base deficit of 15 mmol/L or worse

Patients will be excluded from the study by the following exclusion criteria:

1. Age <18 years
2. Known pregnancy
3. Pulseless traumatic arrest during hospitalization
4. Imminent death precludes resuscitation efforts
5. Isolated head trauma, penetrating or blunt
6. Combined multisystem and head trauma with clinical findings consistent with significant mass effect (e.g., severe coma, lateralizing signs, posturing, or pupillary dilatation secondary to uncal herniation)
7. Hospitalization >60 minutes prior to infusion
8. Known objection to the use of blood, blood products
9. Known injury time >4 hours prior to infusion

Statistical Approach

Approximately 850 patients will be needed to show a 25% reduction in mortality (i.e., from 40% to 30%). A Cox proportional hazards model will be used to determine the impact of DCLHb on mortality while adjusting for demographic and pre-treatment covariables documented as predictors of mortality. Interim monitoring will occur at 10%, 25%, 50%, 75% and the final analysis at 100% enrollment of the 850 patients.

Safety Monitoring

An independent Data Monitoring Committee (members not affiliated with Baxter Healthcare) will be established by the sponsor. Ongoing safety monitoring will be performed by this committee during the enrollment of study patients. If major safety concerns arise, the study can be amended or put on hold until these concerns are addressed.

Informed Consent

The consent procedures followed in the protocol will follow 21 CFR 50.24 "Exception from informed consent requirements for emergency research". These regulations will be utilized based on the favorable risk/benefit profile of DCLHb and the frequent lack of feasibility in obtaining prospective informed consent in this patient population.

Attachment 6

MOVIES

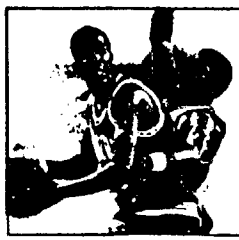
Famous film quotes are real winners

Life & Leisure, D1

WEEKEND

Classical quartet adds a new twist

55hours PLUS



BOYS BASKETBALL

Seaford, Newark reach state final

Sports, C1

The News Journal

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40¢ New Castle County stores, 50¢ all other stores

FRIDAY March 14, 1997 L

FINAL EDITION

Medical Center of Delaware takes part in a new clinical study

You are invited to hear about an important new national clinical research study, cleared by the U.S. Food & Drug Administration, happening at Christiana Hospital's Level I Trauma Center.

Diaspirin Cross-Linked Hemoglobin is a new, investigational blood solution which will be given to randomly selected trauma patients with life-threatening injuries who are in shock from blood loss.

Join members of our Trauma Team to find out why this study could have a profound impact on the future of emergency medical care and could help save lives. Learn what you need to know about the new FDA regulations on exception from informed consent ("waived consent"). The new waived consent may be used if you and your family members are not available to give consent and the medical team treating you determines that participation in this investigational study could improve your chances of survival.

Speakers:

Glen Tinkoff, M.D.
Director,
Trauma Service

Jerry Castellano, PharmD.
Director, Institutional
Review Board

Dates/Times/Places:

March 18, 1997, 7 p.m.,
Riverside Medical Arts
Complex Conference
Center

March 19, 1997, 7 p.m.,
Christiana Hospital
Emergency Center
Conference Room

Phone our Call-a-Nurse service at 428-4100 to reserve your seat today.

Christiana Hospital
MEDICAL CENTER OF DELAWARE

X-613, 3/97

BANKING

First Union to take thumb prints

Business, B7

STATE TOURNAMENT

Hodgson, Howard, Newark, Seaford win

Sports, C1

FOOD

Bring home the flavors of India

Life & Leisure, D1

The News Journal

©1997, The News Journal Co. A Gannett newspaper Wilmington, Del. 119th year, No. 10

WEDNESDAY March 12, 1997

40¢ New Castle County stores, 50¢ all other stores

FINAL EDITION

ATTACHMENT 6

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Christiana Hospital
MEDICAL CENTER OF DELAWARE

X-613, 3/97

RECREATION

Your guide to summer camps

Life & Leisure, J1

INVESTMENT CONTEST

See if you're an early leader in stock game

Business, F1

HIGH SCHOOL BASKETBALL

Titles to St. Mark's girls, Seaford boys

Sports, D1

Sunday News Journal

©1997, The News Journal Co. A Gannett newspaper Wilmington, Del. 23rd year, No. 11

SUNDAY March 16, 1997 $1.50 FINAL EDITION

Sunday News Journal, Wilmington, Del. March 16, 1997 Section **B**

▶CROSSROADS: Baseball season is almost here, and Blue Rocks fans are grabbing tickets. **B3**

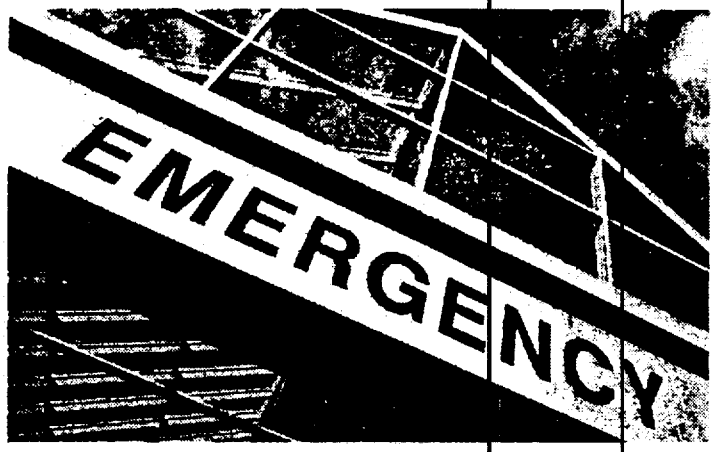
Local

INSIDE:

Have a Local news tip? Call 324-2774.

Medical Center of Delaware takes part in a new clinical study

You are invited to hear about an important new national clinical research study, cleared by the U.S. Food & Drug Administration, happening at Christiana Hospital's Level I Trauma Center.



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Christiana Hospital
MEDICAL CENTER OF DELAWARE

X-613, 3/97

Attachment 7

MEDICAL CENTER OF DELAWARE RESEARCH INSTITUTE

TUESDAY, MARCH 18, 1997
WEDNESDAY, MARCH 19, 1997

AGENDA

The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock

I.	Introduction	*Patty McGraw, RN* Research Coordinator Medical Center of Delaware
II.	Overview of Research Study	*Dr. Glen Tinkoff* Director of Trauma Department of Surgery Medical Center of Delaware
III.	Role of the Institutional Review Board Waiver of Consent	*Dr. Jerry Castellano* Director, Institutional Review Board Grant Administration Medical Center of Delaware

A question-and-answer session will follow the presentation.

Refreshments are available in the back of the room.

Questions From Community Meeting of 3/18/97

1. What is your procedure for enrolling an unconscious patient?
2. Would an advance directive or a directive in one's belongings suffice to serve as a no blood transfusion request?

Eight community members attended. Five members were Jehovah Witnesses. We were unable to idenify the others.

Questions From Community Meeting of 3/19/97

1. How will the enrollment be introduced to the families?
2. What is the trade name of the product?
3. At what point does the pressor effect peak out?
4. Does this solution leak out into the tissues?
5. Does age affect the effectiveness of the blood? Does fresh blood work equally or better than expired blood?
6. How will the randomization be done? Will a telephone call have to be made?
7. What is it about this product that makes you want to use it?
8. How far ahead is the European sites in comparison to us?
9. How are you going to identify Jehovah Witnesses?
10. Will DCLHb effect ABG's?

Eight community members attended. These members consisted of nurses, blood bank employees and others.

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Date 05/01/97

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Company BAXTER HEALTHCARE/H G SCI CTR

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City ROUND LAKE State IL Zip 60073

2 Your Internal Billing Reference Information 716-711-136

3

Recipient's Name ATTN: Doctor [illegible] Phone (301) 827-3524

Dept/Floor/Suite/Room

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4a Express Package Service *Packages under 150 lbs.*

Delivery commitment may be later in some areas.

☒ FedEx Priority Overnight (Next business morning)

☐ FedEx Standard Overnight (Next business afternoon)

☐ FedEx 2Day* (Second business day)

☐ NEW FedEx First Overnight (Earliest next business morning delivery to select locations) (Higher rates apply)

* FedEx Letter Rate not available. Minimum charge: One pound FedEx 2Day rate.

4b Express Freight Service *Packages over 150 lbs.*

Delivery commitment may be later in some areas.

☐ FedEx Overnight Freight (Next business-day service for any distance)

☐ FedEx 2Day Freight (Second business-day service for any distance)

☐ FedEx Express Saver Freight (Up to 3 business-day service based upon distance)

(Call for delivery schedule. See back for detailed descriptions of freight products.)

5 Packaging

☒ FedEx Letter* ☐ FedEx Pak* Declared value limit $500 ☐ FedEx Box ☐ FedEx Tube ☐ Other Pkg.

6 Special Handling

Does this shipment contain dangerous goods?

☐ Yes (As per attached Shipper's Declaration) ☐ Yes (Shipper's Declaration not required)

☐ Dry Ice Dry Ice, 9, UN 1845 III ____ x ____ kg. 904 (Dangerous Goods Shipper's Declaration not required)

CA ☐ Cargo Aircraft Only

7 Payment

☐ Obtain Recipient FedEx Account No.

Bill to: ☒ Sender (Account no. in section 1 will be billed) ☐ Recipient ☐ Third Party ☐ Credit Card ☐ Cash/Check

(Enter FedEx account no. or Credit Card no. below)

Total Packages	Total Weight	Total Declared Value*	Total Charges
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* When declaring a value higher than $100 per shipment, you pay an additional charge. See SERVICE CONDITIONS, DECLARED VALUE AND LIMIT OF LIABILITY section for further information.

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